REMARKS

Claims 1-8 and 15-18 are currently pending.

Claims 1-5 and 15-17 are amended as shown above, without prejudice. Support for the amendments can be found, e.g., on page 4, final paragraph, and page 5, first paragraph, of the specification as filed as well as the Sequence Listing submitted with the application. Applicants submit that no new matter has been added by virtue of this amendment.

Claims 9-14 and 19-20 were previously canceled without prejudice in response to the Restriction Requirement.

Applicants acknowledge and appreciate the withdrawal of the rejection under 35 U.S.C. 112, second paragraph, and the rejections under 35 USC 112, first paragraph, (enablement rejections, items 6 and 9 as set out in the previous Office Action), in view of the arguments and amendments previously submitted in response to that Action.

Indefiniteness Rejections

Claim 3 remains rejected under 35 U.S.C. 112, second paragraph, for its recitation of both open language ("having") and closed language ("consisting of"). Applicants respectfully disagree with the assertion in the Office Action that such language is confusing because the open language and closed language refer to different antecedents. Nevertheless, in order to expedite prosecution of the instant application to allowance, claim 3 has now been amended to remove the recitation of both open language and closed language. Specifically, claim 3 now recites a method of detecting cancer wherein the N-terminus is "a peptide fragment *consisting of* the amino acid sequence from the 1st amino acid to the 358th amino acid of SEQ ID NO:4" (emphasis supplied).

Applicants believe amended claim 3 obviates any confusion as to the peptide fragment being detected at the N-terminus of GPC3, and believe the claim is clear and definite. Thus, applicants respectfully request reconsideration and withdrawal of the rejection of claim 3 under 35 U.S.C. 112, second paragraph.

Enablement Rejections

Claims 1-8 and 15-18 remain rejected under 35 U.S.C. § 112, first paragraph. The Office Action first states that the claimed method would not distinguish between detection of cancer and liver cirrhosis or (in a separate rejection) melanoma because one cannot predict that detection of an increased level of soluble GPC3 in serum as compared to control indicates the presence of cancer.

In response, applicants note that the present invention is directed to a method for detecting (not diagnosing) the presence of cancer in a subject, regardless of the presence or absence of liver cirrhosis or melanoma in that subject. Based on the experiments carried out in support of the claimed invention, applicants believe the method *is* predictive of detecting cancer in a patient. Specifically, Example 3 of the present specification describes the experiment, wherein, using the claimed method, "[t]he soluble GPC3 was detected ... in the sera of the mice" 53 days after HepG2 human hepatic cancer cells had been grafted into the mice (when tumor mass had been successfully formed.) The concentration of purified soluble GPC3 in the mice with tumors was 23 to 90 ng/ml, in contrast to the control mouse sera, wherein the level of purified soluble GPC3 was "below the detection limit." See, pages 42-44 of the present specification.

Thus, applicants maintain that it is not necessary to distinguish between cancer and cirrhosis or melanoma. In other words, a subject who shows an increased level of GPC3 as detected by the invention may also have cirrhosis or melanoma, or may not. Applicants therefore submit that the specification, at the very least, establishes a predictive correlation between a greater level of soluble GPC3 in sera and the presence of in vivo tumor, as compared to normal control, and thus detection of cancer is established, as claimed.

In addition, the claimed method comprises "detecting a soluble GPC3 protein level in a test sample, and determining whether said detected soluble GPC3 level is greater than a

normal control level of GPC3." Thus, the recitation of a "basal level," which the Examiner considered unclear, has been replaced with the more specific recitation of "normal control."

Further, the claimed method of detecting cancer by determining increased levels of soluble GPC3, as compared to normal controls, has been demonstrated in human patients having hepatic cell cancer. The protocol and results of the experiments carried out in these human subjects is presented in Appendix A of Dr. Matsuura's expert declaration submitted under 37 CFR 1.132, wherein Dr. Matsuura confirms that over-expression of soluble GPC3 is frequently and predictably detected in human patients with hepatic cancer.

Thus, applicants respectfully submit that one skilled in the art would be enabled to practice the claimed invention without any additional guidance than the specification and without any undue experimentation. Therefore, applicants respectfully request withdrawal of the enablement rejection, under 35 USC 112, first paragraph, of claims 1-8 and 15-18.

New Rejections

Appendix A, previously submitted, is objected to for having no title or recitation showing that the data is actually GPC3 protein concentration from serum of normal human control and patients with hepatic cancer. Appendix A is resubmitted herewith, as part of an expert declaration under Rule 132 by Dr. Matsuura, which expressly states, and therefore establishes, that the data is from GPC3 protein concentration from serum of human patients – either a normal control patient or patients with hepatic cancer. Reconsideration and withdrawal of the objection to Appendix A is respectfully requested

In addition, claim 3 is rejected under 35 USC 112, second paragraph, as being indefinite because a sequence identification number for GPC3 is needed for reference of the particular amino acids recited. Claim 3, as amended in this Reply, now reads as follows:

> 3. The method of claim 2, wherein the N-terminal peptide of GPC3 is a peptide fragment consisting of the amino acid sequence from the 1st amino acid to the 358th amino acid of SEQ ID NO: 4. (emphasis supplied)

Thus, the sequence identification number, namely SEQ. ID NO. 4, is expressly recited within claim 3 and provides reference for amino acids 1-358 of the N-terminal peptide. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC 112, second paragraph, of claim 3.

CONCLUSION

An early and favorable action on the merits is earnestly solicited. The Examiner is respectfully requested to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,
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By: _____
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